Author's response to reviews

Title: A modelled economic evaluation comparing atomoxetine with methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder in Spain

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Author's response to reviews: see over
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Dear Sir/Mdm,

Re the resubmission of the manuscript: "A modelled economic evaluation comparing atomoxetine with methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder in Spain" by Jihyung Hong et al.

We thank the journal for the opportunity to conduct a revision on the above paper and hereby resubmit a revised version incorporating suggestions made by referees. Our responses to the reviewers are as follows:

Response to Referee 1:

In the following, I will focus on essential revision needs. A minor point relates to the omission of a note on the cost effectiveness of long acting medications for ADHD, which appeared in European Child + Adolescent Psychiatry in 2007. This note stated that methylphenidate is associated with equal or better symptomatic response compared to atomoxetine and, on this ground, the treatment with lower costs is preferred.

- The note states that methylphenidate is associated with equal or better symptomatic response compared to atomoxetine and, on this ground, the treatment with lower costs is preferred.
- We have also acknowledged that methylphenidate has equal or better efficacy on page 3 (Background) and page 14 (Discussion). However, the fact that (1) atomoxetine is associated with a more stable and longer lasting response than methylphenidate during a day (i.e. throughout a night till the following morning), (2) it is a non-stimulant, and (3) it has adverse event profile without insomnia led to the higher utility values associated with atomoxetine in the utility valuation study (Secnik et al., 2005). Although the health states descriptors used in the utility survey are derived largely based on clinical trial data and validated by clinical measures.
experts, we have further discussed the limitations associated with them (see page 14 & 15).

Minor essential revisions

- The cost effectiveness of a medication management strategy for ADHD in children and adolescents has been evaluated in a number of studies addressing the impact of coexisting conditions (e.g., Foster et al., 2007; and others), which were based on the major study in the field, the NIMH supported MTA Study. These findings might be discussed.

- We do recognise that coexisting conditions can exert a significant influence as well. Therefore our study has been also conducted separately for the subgroup with co-morbid conditions, where methylphenidate (stimulants) is often contraindicated. We noted however that this population could benefit more from behavioural treatments (probably combined with medications). This point has been further discussed in the text (see page 15).

- While the NICE ADHD assessment has been quoted to support the authors’ claim that there is no identifiable difference in effectiveness between atomoxetine and methylphenidate (p. 3), the critique that this assessment did not make full use of the available clinical evidence (see Schlander, Health Technology Assessments by NICE…, New York: Springer 2007). In fact, other analyses did report differences in favor of methylphenidate (Steinhoff, 2003; Faraone, 2003; Faraone et al., 2003, 2006; for a discussion, you may refer to Schlander, 2007, pp. 132f.). Of note, however, all these studies (including the present one) are limited in scope due to their primary focus on symptomatic improvement. Therefore, the importance of functional improvement of patients (and outcomes beyond those mentioned) should be discussed in more depth.

- The NICE offers a range of cost-effective choices that would benefit various subpopulations of those suffering from illness including ADHD. Although the symptomatic improvement was found to be higher for methylphenidate in some studies as pointed by the referee, it was just one aspect of the benefits (which is still very important).

  However, our study included utility as health outcome, which in general covers more broad benefits of treatments than just symptomatic improvement, reflecting patient preference. With the reasons mentioned above (see the response for the first question), atomoxetine was preferred to methylphenidate. Nevertheless, we noted the limitations of using these utility values and highlighted them in our discussion (see page 14 and 15).

Major compulsory revisions

- The present study has been focused on symptomatic response rates, which were subsequently transformed into QALYs using utility weights for responders and nonresponders. It is not clear what evidence provides the basis for the assertion that “the nature of response with atomoxetine, which was reflected in the health state descriptors used in the utility valuation study, is preferred to that of stimulant treatments” (cf. Cottrell et al., 2008, p. 386). The authors should address this issue and, for the present manuscript to be accepted for publication,
be able to persuade readers of the manuscript that the “rigorously conducted utility valuation study” – supported by the manufacturer of atomoxetine – did not fabricate the results needed for an economic evaluation showing acceptable cost effectiveness of atomoxetine.

- We are in agreement that the utility values used require further validation. The nature of response refers to the behavioural management throughout a day. Patients responding to atomoxetine appeared to experience a more stable and longer-lasting response (throughout a night till the following morning) than those responding to methylphenidate. In addition, parents of the ADHD tended to prefer non-stimulants to stimulants when the rest is the same otherwise. These have been reflected in the utility values. However, we admit that caution is required when interpreting these utility values since there is no large trial to confirm and validate the health states descriptors used to elicit the utility values. Furthermore, we do recognise the concerns over the use of utilities (and therefore QALYs) for the paediatric population. This is because ADHD children tend to underestimate their ‘disease-specific problems’ while the validity of utilities elicited with parent proxies has not been fully understood yet. Therefore when data become available from sufficiently powered randomised controlled trials, the validation of these utility values is necessary. This has been discussed in the text as well (see page 14 and 15).

- Background: According to the NICE assessment (King et al., 2004, p. 240), “the review … highlighted some concerns about the validity of these estimates, [note added: referring to these utility estimates] particularly the fact that the utility of a non-responder without side effects differs between treatments. For example, the utility associated with non-response to atomoxetine, without side effects, is estimated to be 0.902, which compares to an estimated utility of 0.880 associated with non-response and no medication. A difference in utility of 0.022 is relatively large in this population, particularly between health states with identical characteristics. … so the sensitivity analysis uses the utility of non-response associated with no medication.” Interestingly, the cited study (Secnik et al., 2005) also reported a higher utility (of 0.886) for atomoxetine “nonresponders” with side effects than for “responders” without medication (0.880; poster presentation by Secnik et al., 2004, at ISPOR meeting in Arlington, Virginia; cf. also NICE assessment report by King et al., 2004, p. 217). Since then a series of closely related papers (Matza et al., 2004, 2005; in addition to Secnik et al., 2005) has appeared in various journals, reporting details on the elicitation of those standard gamble scores. As it turns out, the description of health states (Secnik et al., 2004, 2005; cf. also NICE assessment report, appendix 10, pp. 359-366) for patients treated with stimulants with “no side effects” includes symptoms associated with insomnia, which has been listed as a “side effect” separately in the description of corresponding health states “with side effects” – which may amount to double-counting and is the only conceivable explanation for the twice as high differences in utility gains reported with nonstimulants (i.e., atomoxetine; difference, 0.06) compared to stimulants (i.e., methylphenidate immediate-release; difference, 0.02; or methylphenidate-extended-release, difference, 0.03). As mentioned earlier, this series of experiments was conducted under contract with the manufacturer of
atomoxetine and should be interpreted with caution. As to the present study, these observations appear highly relevant since (a) it is also sponsored by the manufacturer of atomoxetine and (b) it is heavily building on these data. These issues were also identified previously in the NICE monograph (Schlander, Springer, 2007, p. 61), and these concerns should be adequately addressed by the authors of the paper under consideration.

- Regarding insomnia, it was included in the health state descriptors used to elicit the utility values. As pointed out, this (alongside parents’ preference of non-stimulant when the rest is the same) might be one of the key drivers to lead the higher utility values for atomoxetine non-responder in comparison with those for methylphenidate non-responder. However, we do believe that there is no double counting of this impact. This is because insomnia in the model is used only as a transition probability that affects time to switch to another alternative. This logic applies to most of economic evaluation studies. For example, when we evaluate the cost-effectiveness of antipsychotics, we would consider the transition probabilities of relapse and/or remission and also the health states of relapse and/or remission separately.

  In addition, sensitivity analyses in which the impact of insomnia was removed (i.e. its transition probability set at zero) showed no differences in the results. In fact, in our analysis, patients could switch from atomoxetine to methylphenidate and vice versa as a second-line treatment when the first-line treatment failed. This means that the impact of insomnia on the results would be lessened as its influence was present in both treatment arms (either as first line or second line treatment). This also implies that if the insomnia influences the time to next alternative and thus leads to switch to atomoxetine from the first line treatment of methylphenidate (though its impact would be rather negligible), this would ironically help to increase the overall utility values of the methylphenidate arm as atomoxetine is associated with higher utility values in the present economic model.

Response to Referee 2:

The aim of the present study was to estimate the cost-effectiveness of atomoxetine compared to methylphenidate (MPH) in the treatment of ADHD among children and adolescents. The study is based on an economic model to compare the costs and benefits of atomoxetine to that of either MPH or ‘no medication’ in the Spanish context. It thus adds essential information and directives on the interface between economy and medical treatment guidelines. Child psychiatry is in great need of comparing cost efficacy of alternative treatments, especially in terms of ADHD, now that non-addictive and easy usable compounds become available. Although they are more expensive, the question whether it is efficacious and cost efficient to use a relatively new compound is important and should be explored.

- When analyzing external validity, we miss information on decisions of ethics committees. Since the clinical data was based on a review of controlled clinical trials and other clinical literature, the study type can be described as a meta-analysis applying a specific economic model to the entity of specific existing data. It is of utmost importance to outline the limitations of meta-analysis
studies, comprising the same potential for bias as the smallest of clinical studies. In this context, the statement that data was validated by international experts doesn’t seem sufficiently elaborated and needs more illustrations of the contents of these validation procedures.

- We have conducted the economic evaluation mostly based on clinical trials. As pointed out, some of point estimates (for safety outcomes) have been drawn from meta-analyses by synthesising the data available as there is no big trial to provide robust point estimates. As this is a standard procedure in the economic evaluation, we have not discussed the limitations associated with data synthesis (including meta-analyses).
- The ‘validation by experts’ in the text refers to the creation of the descriptors for health states only. Based on these descriptors, Secnik et al. (2005) conducted the utility valuation survey, and we used those utilities elicited by them. All other clinical data in our model (other than the descriptors) are directly drawn from clinical trial data. Therefore we have not elaborated ‘the validation by experts’ as it is not relevant in our case, though we have discussed the limitations associated with the utility values used (see page 14 and 15).

In terms of internal validity, we would recommend providing more information on sensitivity analyses. Additionally, the fourteen possible health states included in the economic model are not described transparently enough. The four domains of which the health states are comprised should be depicted in more detail, elucidating which methods were used to gain information on descriptors referring to behavior during different time periods throughout the day, information concerning the child’s overall social well-being, attributes regarding medication regimen (e.g. frequency of administration) and medication-related adverse events.

- We have conducted a series of sensitivity analyses on costs, transition probabilities (adverse events-related rates, discontinuation rates, relapse rates and response rates) and utilities. However, we have not reported the detailed results of the sensitivity analyses other than that of utility values. This was because the results were more or less insensitive to changes in other key inputs as noted in both results and discussion. As mentioned in the text (see page 12), those results are available upon requests. Nonetheless, we have attached the results of sensitivity analyses for reviewers only.
- As the details of the four domains can be found elsewhere (i.e. original utility survey by Secnik (2005)), we have not provided further details. We have, however, stated the reference more clearly, and also mentioned the main driver for the difference in the utilities between atomoxetine and methylphenidate responders (please see page 8).

Furthermore, it seems essential to give more information on the issue of the costs involving the non-drug using population.

- We agree that there would be some implications in involving the non-drug using population when examining costs. In our analysis, the cost for this population was assumed to be ‘zero’ as we only considered the direct costs (i.e. that of
medications in this case) while assuming the same ‘non-drug’ costs for both active treatment arm and ‘no drug’ arm. The exclusion of indirect costs, however, may be biased against active treatment as effective treatments are likely to decrease these costs. As this has been stated in the discussion already (see page 14), we have not made any further comments.